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DETAILED ACTION

Status of the Application

Claims 21, 28, 43, 109-113, 120-135, 137-143 are pending.

Applicant's amendment of claims 21 and 28 as submitted in a communication filed on 8/3/2011 is acknowledged.

Claims 43, 109-113, 120-135 and 137-143 are withdrawn from consideration as being directed to non-elected subject matter. Claims 21 and 28 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this rejection can be found in a prior Office action.
2. Claims 21, 28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Choulika et al. (U.S. Publication No. 20020107214, U.S. Application No. 10/917295 filed on 7/27/2001) in view of Bibikova et al. (Molecular and Cellular Biology 21(1):289-297, 2001) and further in view of Takeuchi et al. (Biochemical and Biophysical Research Communications 293:953-957, 2002).
3. This rejection has been extensively discussed in prior Office actions. It is maintained for the reasons of record and those set forth below.
4. Applicant argues that the claims require a single vector that encodes two zinc finger nucleases that dimerize and cleave an endogenous gene, wherein the vector also comprises a repair substrate and a nuclear localization signal. Applicant submits that Choulika et al. fails to teach a vector that encodes the requisite nuclease and/or includes a nuclear localization signal and also fails to teach or suggest cleavage of endogenous genes. Applicant argues that Choulika et al. uses ScaI to cleave sites artificially integrated in the chromosome. With regard to Bibikova et al., applicant argues that Bibikova et al. only disclose

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microinjection of the chimeric nucleases, do not teach a vector comprising the repair substrate but rather injection of the repair substrate, do not teach a target site in an endogenous gene, and injected substrates in *Xenopus* oocytes is not predictive of endogenous genes in mammalian cells. With regard to Takeuchi et al., applicant submits that they failed to teach a vector comprising a repair substrate and a nucleic acid encoding at least two zinc finger nucleases.

5. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). With regard to the teachings of Chouluka et al., and Bibikova et al., it is noted that it is the combination of the teachings of Chouluka et al., and Bibikova et al. that provide a vector encoding two chimeric nucleases each comprising a zinc finger DNA binding domain and a FokI cleavage domain and the repair substrate and a cell comprising and expressing said vector. The nuclear localization signal is provided by the teachings of Takeuchi et al. Therefore, it is the combination of references that render the claimed invention obvious.

With regard to the "endogenous mammalian gene" limitation, it is noted that contrary to applicant's assertions, the prior art clearly suggests targeting an endogenous mammalian gene. The entire purpose for inserting an artificial cleavage site in the chromosome as disclosed by Chouluka et al. was to show that one could target a site in the chromosome of an organism, including human cells, for repair of a specific sequence. Similarly, while applicant criticizes the teachings of Bibikova et al. as being limited to the injection of the chimeric nuclease into the oocytes, it is reiterated herein that the goal of the work described by Bibikova et al. was to show that in the presence of the chimeric nuclease, one could repair endogenous genes in the cell. It may be that the chimeric nucleases of Bibikova et al. were not expressed intracellularly but rather delivered to the desired site. However, this does not take away from the fact

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Bibikova et al. were able to show that in the presence of the chimeric nuclease and the repair substrate, targeted homologous recombination occurs intracellularly. There is nothing unpredictable with regard to constructing a vector once all the structural features in that vector are known since the methods to manufacture a vector are well known and widely used in the art. Also, there is nothing unpredictable about transforming a mammalian cell with that vector. There is a reasonable expectation of success at (i) obtaining expression in a mammalian cell of the chimeric nucleases encoded by the vector, and (ii) homologous recombination with the repair substrate intracellularly, as suggested by the results obtained by Choulika et al. in mammalian cells and Bibikova et al. in *Xenopus* oocytes. Therefore, contrary to applicant's assertions, the teachings of Choulika et al., Bibikova et al. and Takeuchi et al. render the claimed invention obvious.

Conclusion

6. No claim is in condition for allowance.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

8. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the

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notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

9. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached at (571) 272-0956. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner
Art Unit 1652

DR
October 12, 2011